UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/719,045	12/07/2000	Andrew Paul Chapman	CARP-0086	3379

34133 7590 03/24/2004

COZEN O'CONNOR, P.C.
1900 MARKET STREET
PHILADELPHIA, PA 19103-3508

EXAMINER	
SAUNDERS, DAVID A	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
719,045	CHAPMAN et al
Examiner SAUNDERS	**Group Art Unit** 1644

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 12/4/03.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-15 is/are pending in the application.

Of the above claim(s) 8-9 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-7, 10-15 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____ .

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

Amendment of 12/4/03 has been entered. Claims 1-15 are pending, with claims 1-7 and 10-15 under examination.

Applicant's amendment has overcome previously stated objections to the specification and claims. Examiner concurs that claim 3 previously was dependent from only claim 1.

Receipt of an abstract is acknowledged.

Claims 1-7 and 10-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 2 are confusing by reciting "increasing the circulating half life of said fragment." One does not know what the structural features of the molecule(s) are that do not have an increased half-life. Are these molecules ones that do not have any polymer molecules attached; are these ones that have merely a disulfide interchain bridge? The claim must define some basis against which the "increasing" can be measured.

Claims 1-7 and 10-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1 and 2 recite new matter.

The inserted claim language "effective for increasing the circulating half life of said fragment" is overly broad because it does not stipulate that the "increasing" is in

comparison to "other antibody fragments which have the same number and type of polymer molecules but in which in the polymer molecules are randomly attached" as recited in the abstract (that submitted 12/4/03 has the same content as the PCT stage abstract). This same concept is conveyed at specification page 3, lines 20-23, and the examiner cannot see where applicant has disclosed more broadly regarding the features of the instant invention.

Applicant has urged that page 2, lines 1-14 support the language inserted by amendment. The examiner does not consider this portion of the disclosure as supporting, because it is merely a general review of the state of the art, not of the particular features of applicant's contribution over the prior art.

Applicant has also urged that Table 2 and Figure 5 support the amendment. The examiner is unable to evaluate these tables and figures because it is unclear what the abbreviations "DFM", "DFM-PEG", etc. mean. The text does not adequately explain these. In any event, it appears that applicant's examples were intended to make a comparison of the conjugate of the invention with an anti-PDGFBR DFM that was "derivatised with PEG randomly" as deemed by the examiner supra.

Claims 1-7 and 10-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant did not possess the

genus of divalent antibody fragments having a covalently linked polymer effective for increasing the circulating half-life of the fragment.

Applicant's disclosure has attempted to encompass anything and everything in terms of the nature of the inter-chain bridge (or linker) and in terms of the polymer covalently attached thereto.

It is not clear whether the purpose of applicant's disclosed feature of covalently linking the polymer to the inter-chain bridge is for i) improving affinity/avidity/specificity, or ii) for improving pharmacokinetic properties,or iii) for improving both of these.

If it is taken that both i) and ii) need not be improved, then it is not clear where applicant's disclosure defines a line of demarcation between those polymers that do and those that do not increase the circulating half-life. Applicant has stated that the polymer can be part of the bridge, which can be as small as a C4-C20 alkylene chain. Applicant has considered that the "polymer" can have an average molecular weight range from a value as small as "around 500Da" (page 6 line 30). It is noted that applicant's review of the state of the art at pages 2-3 refers to larger size polymers, such as PEG, as having been used to improve pharmaco-kinetics/extend circulating half life, one of skill would reasonably doubt that the smaller polymers disclosed by applicant would have any significant effect upon the circulating half-life when conjugated to the antibody fragment. Given the lack of specific direction provided by applicant one of skill could not readily envision the structural and size characteristics of those polymers which do and those that do not increase circulating half-life, except for what applicant has exemplified in terms of 10K, 20K and 40K PEG. For example, if it were roughly assumed that

increased area under curve (AUC) value of Table 2 is linearly related to the m.w. of the PEG, then a 500Da or 1000 Da PEG (at lower end of applicant's disclosed range at page 6, line 30) would only increase the AUC value by a mere 1 or 2% respectively. Such would not provide for any significantly observable improvement over the AUC valve of 4.4%, disclosed in the right hand col. of Fig. 2.

In addition to size considerations, applicant's disclosure has done little to set forth what other properties of the polymer are important in contributing to an increase in circulating half-life. For example applicant considers that polyalkylenes and polyakenylenes can be used as the polymer (page 6, lines 10-11); these have no charge and no polar groups. Applicant has also considered that homo or heteropolysaccharides may be used (page 6, lines 11-12); the former would include dextran, which is polar but not charged; the latter would incompass heparin, which is both polar and charged. Applicant has set forth no common recognizable structural properties of the polymers which confer increased circulating half-life. By disclosing anything and everything, applicant has disclosed nothing but what he has exemplified.

In essence, applicant's language inserted into claims 1 and 2 is nothing more than a claiming of a subgenus of conjugates in terms of a functional property not linked to any common structure. This is not adequate to meet the description requirement of 35 USC 112, first paragraph. Reagents of UC V. Eli Lilly & Co. 43 USPQ 2d 1398.

Claims 1-7 and 10-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant's invention is not enabled. The above particular issue of description raises an issue of enablement.

As noted supra under description, applicant has set forth no common features, in terms of molecular size, of polarity, of charge, etc., which distinguish those polymers that confer increased circulating half-life from those polymers that do not. Due to possible complexe interactions between these variables applicant is asking one to conduct trial and error experimentation.

The prior art rejections of record have been withdrawn. Rhind et al and Huston et al teach nothing about extension of circulating half-life. Their linking chains are suffieciently small and unlike PEG that the examiner reasonably considers these linkers would not enhance the circulating half-life.

More pertainent prior art is cited infra.

Claims 1-7, 12-13 and 15 are rejected under 35 U.S.C. 102(e) as being entirely anticipated by Gonzales et al (6,025,158).

Gonzales et al teach antibody fragments having an extended circulating half life by virtue of being conjugated to a high m.w. polymer—e.g. PEG of 20,000 D or greater. Gonzales et al disclose embodiments in which two or more Fab, Fab' or Fab'-SH fragments are covalently conjugated to a polymer backbone. The polymer thus links the antibody fragments. See especially col. 35, lines 40-57; col.41, lines 41-62. A preferred site of conjugating the polymer to the antibody fragment is at the hinge region of the

latter; see col.35, lines 6-13. In embodiments in which the number of Fab, Fab' or Fab'-SH fragments is two and the number of polymer members is one, instant claims 1-3 are anticipated.

Regarding claim 4, the embodiment in which Fab' or Fab'-SH fragments are employed is consistent with the claim. See col.11, lines 57-64 for teachings of the structures of these fragments.

Regarding claim 5, note teaching of linking to the hindge region (col.35 lines 20-21) and of linking via a sulfhydryl reactive moiety attached to PEG (col.42, lines 12-18). Note also the compling chemistry exemplified at col. 120, line 15-col.122, line 31.

For claims 6-7, note teachings of preferred polymers at col. 41, lines 8-25.

With respect to claim 12, note Gonzales et al. teach conjugation of label/reporter groups at col. 44, line 5-col.45, line 14.

Regarding claim 13, the IL-8, for which the exemplified antibodies of Gonzales et al are specific, is a soluble antigen, secreted by cells (col.1, lines 44-45).

For claim 15, note col.45, lines 22-25.

Claims 1 and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzales et al in view of Barbanti et al (5,436,154).

Gonzales et al have been noted supra for generically teaching the coupling/bridging of Fab, Fab' or Fab'-SH antibody fragments of generic binding specificity, or more particularly of IL-8 binding specificity, to a polymer to extend circulating half-life.

Barbanti et al teach antibodies to TNF-alpha, including fragments of such antibodies (col.5, lines 44-55). It would have been obvious to conjugate these antibody fragments of Barbanti et al to PEG in the manner taught by Gonzales et al, in order to also extend half life of the antibodies. One of skill would have been reasonably motivated to consider both references, because both IL-8 and TNF-alpha are involved in inflammation and because increasing the circulating half life of an antibody to any mediator of inflammation would have been expected to permit more of the administered antibody to bind the mediator.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Saunders, PhD whose telephone number is

571-272-0849. The examiner can normally be reached on Monday-Thursday from 8:00 a.m. to 5:30 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Saunders/tgd

March 19, 2004

David A Saunders

DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT ~~182~~ 1644